CLAIMS

We claim:

1. A method of detecting an interaction among agents in a group using a fixed- ratio ray design and determining whether subsets of said agents also interact, comprising the steps of

a. determining an additivity model from single chemical data;

b. fitting a mixture model in terms of total dose to mixture data from fixed-ratio rays;

c. statistically comparing said additivity model to said mixture model, wherein a difference between said additivity model and said mixture model indicates an interaction among said agents in said group;

d. removing at least one subset of agents from said group, wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

e. repeating steps b and c for agents remaining in said group after removal of said subset; and

f. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray mixture models.

2. The method of claim 1 wherein said method is applied to a plurality of full-ray groups.

3. The method of claim 1 further comprising the step of carrying out steps b and c for said subset of agents.

4. The method of claim 1, wherein said additivity model is graphically represented as an additivity curve and said mixture model is graphically represented as a mixture curve in terms of total dose.

5. The method of claim 1, further comprising the step of determining simultaneous confidence bands on the difference between said additivity curve and said mixture curve or

between mixture curves on full and reduced rays.

6. A method of detecting, in a group of agents, using a fixed-ratio ray design, the number of agents that interact, and determining whether subsets of said agents also interact, comprising the steps of

a. fitting a suitable polynomial in total dose to experimental data obtained with a combination of said agents;

b. statistically identifying higher order terms of said polynomial that are not equal to zero, wherein the number of agents that interact in said group of agents is equal to the degree of said higher order terms that are not equal to zero;

c. removing at least one subset of agents from said group, wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

d. repeating steps a and b for agents remaining in said group after removal of said subset;

e. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray mixture models.

7. The method of claim 6 wherein said method is applied to a plurality of full-ray groups.

8. The method of claim 6 further comprising the step of carrying out steps a and b for said subset of agents.

9. The method of claim 6, wherein single chemical data are used to estimate an additivity model which is linked to a linear term in said polynomial model.

10. The method of claim 9, wherein an additivity model is graphically represented as an additivity curve and said polynomial model is graphically represented as a mixture curve in terms of total dose.

11. The method of claim 6, wherein said polynomial is embedded in a generalized linear model.

12. The method of claim 6, wherein said polynomial is embedded in a general non-linear model.

13. The method of claim 6, further comprising the step of generating a graphical representation of said polynomial in total dose.

14. A method of determining an interaction threshold for agents in a group, comprising the step of

generating a generalized linear model or general nonlinear model that permits estimation of the boundaries between a region of additivity of said agents and a region of interaction of said agents, wherein said boundaries define said interaction threshold.

15. The method of claim 14, wherein said region of additivity of said agents and said region of interaction of said agents is determined by the steps of

a. determining an additivity model from single chemical data;

b. fitting an interaction threshold mixture model that incorporates an interaction threshold parameter in terms of total dose to mixture data from fixed-ratio rays; and

c. statistically comparing said additivity model to said interaction threshold mixture model, wherein a region of difference between said additivity model and said interaction threshold mixture model indicates a region of interaction among said agents in said group, and a region of coincidence between said additivity model and said interaction threshold mixture model indicates a region of additivity among said agents in said group.

16. The method of claim 15 wherein said method is applied to a plurality of full-ray groups.

17. The method of claim 15 further comprising the steps of

d. removing at least one subset of agents from said group wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

e. repeating steps b and c for agents remaining in said group after removal of said subset; and

f. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray interaction threshold mixture models.

18. The method of claim 15 further comprising the step of carrying out steps b and c for said subset of agents.

19. The method of claim 14, wherein said region of additivity of said agents and said region of interaction of said agents is determined by the steps of

a. determining an additivity model from single chemical data;

b. fitting an interaction threshold mixture model that incorporates an interaction threshold parameter in terms of total dose to mixture data from fixed-ratio rays, wherein said region of additivity is conditioned on results obtained in step a; and

c. statistically comparing said additivity model to said interaction threshold mixture model, wherein a region of difference between said additivity model and said interaction threshold mixture model indicates a region of interaction among said agents in said group, and a region of coincidence between said additivity model and said interaction threshold mixture model indicates a region of additivity among said agents in said group.

20. The method of claim 19 wherein said method is applied to a plurality of full-ray groups.

21. The method of claim 19 further comprising the steps of

d. removing at least one subset of agents from said group, wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

e. repeating steps b and c for agents remaining in said group after removal of said subset;

and

f. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray interaction threshold mixture models.

22. The method of claim 19 further comprising the step of carrying out steps b and c for said subset of agents.

23. The method of claim 14, wherein said region of additivity of said agents and said region of interaction of said agents is determined by the steps of

a. fitting an interaction threshold mixture model parameterized with a polynomial function for regions of interaction to experimental data obtained with a combination of said agents, and

b. statistically testing whether the interaction threshold parameter is different from zero and identifying higher order terms of said polynomial that are not equal to zero.

24. The method of claim 23 wherein said method is applied to a plurality of full-ray groups.

25. The method of claim 23, further comprising the steps of

c. removing at least one subset of agents from said group wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

d. repeating steps a and b for agents remaining in said group after removal of said subset; and

e. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray mixture models.

26. The method of claim 23, wherein single chemical data are also utilized.

27. A method of designing experiments that achieve a target power associated with a test of additivity, comprising the steps of

a. specifying said target power, a significance level, a number of mixture dose groups, and a magnitude of departure from additivity in terms of total dose;

b. setting a candidate total sample size;

c. formulating a design by expressing a design optimality criterion as a function of said target power, said significance level, said number of mixture dose groups, said magnitude of departure from additivity in terms of total dose, and said candidate total sample size, wherein optimal locations of total dose groups and optimal allocations of subjects to said total dose groups are determined using a direct search algorithm;

d. calculating a calculated power associated with said design;

e. comparing said calculated power to said target power; and

f. repeating steps a-e until said step of comparing shows that said calculated power is equal to said target power.

28. The method of claim 27 further comprising the step of increasing said total sample size used during said step of repeating if said step of comparing shows that said calculated power is less than said target power.

29. The method of claim 27 further comprising the step of decreasing said total sample size used during said step of repeating if said step of comparing shows that said calculated power is greater than said target power.

30. Software for causing a computer to carry out a method of detecting an interaction among agents in a group using a fixed- ratio ray design and determining whether subsets of said agents also interact, wherein said method comprises the steps of

a. determining an additivity model from single chemical data;

b. fitting a mixture model in terms of total dose to mixture data from fixed-ratio rays;

c. statistically comparing said additivity model to said mixture model, wherein a

difference between said additivity model and said mixture model indicates an interaction among said agents in said group;

d. removing at least one subset of agents from said group, wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

e. repeating steps b and c for agents remaining in said group after removal of said subset; and

f. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray mixture models.

31. Software for causing a computer to carry out a method of detecting, in a group of agents, using a fixed-ratio ray design, the number of agents that interact, and determining whether subsets of said agents also interact, wherein said method comprises the steps of

a. fitting a suitable polynomial in total dose to experimental data obtained with a combination of said agents;

b. statistically identifying higher order terms of said polynomial that are not equal to zero, wherein the number of agents that interact in said group of agents is equal to the degree of said higher order terms that are not equal to zero;

c. removing at least one subset of agents from said group, wherein relative ratios of remaining agents stay the same as in said fixed-ratio ray design;

d. repeating steps a and b for agents remaining in said group after removal of said subset;

e. determining whether or not said remaining agents interact with said subset of agents by utilizing statistical methods based on algebraic manipulations relating full and reduced ray mixture models.

32. Software for causing a computer to carry out a method of determining an interaction threshold for agents in a group, wherein said method comprises the step of

generating a generalized linear model or general nonlinear model that permits estimation of the boundaries between a region of additivity of said agents and a region of interaction of said

agents, wherein said boundaries define said interaction threshold.

33. Software for causing a computer to carry out a method of designing experiments that achieve a target power associated with a test of additivity, wherein said method comprises the steps of

a. specifying said target power, a significance level, a number of mixture dose groups, and a magnitude of departure from additivity in terms of total dose;

b. setting a candidate total sample size;

c. formulating a design by expressing a design optimality criterion as a function of said target power, said significance level, said number of mixture dose groups, said magnitude of departure from additivity in terms of total dose, and said candidate total sample size, wherein optimal locations of total dose groups and optimal allocations of subjects to said total dose groups are determined using a direct search algorithm;

d. calculating a calculated power associated with said design;

e. comparing said calculated power to said target power; and

f. repeating steps a-e until said step of comparing shows that said calculated power is equal to said target power.